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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,803	01/14/2004	James McSwiggen	MBHB03-465-C (400.142)	5421

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,803	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20 and 28-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20 and 28-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 3/23/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/7/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-20 and 28-38 are pending in the application.

Response to Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120.

In the instant case, the effective filing date is determined to be that of the parent application of PCT/US03/05346, which has an effective filing date of 2/20/03. The instant claims of application 10/757,803 do not receive the benefit of any of the other priority documents, because these documents do not disclose double stranded nucleic acid molecules with a limitation of about 18 to about 27 nucleotides in length wherein about 18 to about 23 nucleotides of each strand are complementary to each other, and at least 19 nucleotides of the second strand are complementary to a target RNA

sequence, wherein each of the instantly recited terminal cap moieties are supported. Thus, the instant claims are accorded an effective filing date of 2/20/03.

Applicant argues that the present application claims priority to 60/358,580 filed 2/20/2002 and points to support for the instant claim limitations in 60/358,580.

Applicant's argument has been considered but is not found persuasive. The priority provisional filed on 2/20/2002 expires within one year. There are no documents that arose from 60/358,580 for which priority is being claimed that recite the instantly claimed limitations listed above. The intervening references do not recite each of the instant limitations and therefore the instant application does not receive benefit of 60/358,580.

PCT/US03/05346 did not arise from 60/358,580, and therefore does not receive benefit of this document.

Response to Claim Rejections - 35 USC § 103

The arguments filed by applicant that are considered pertinent to the instant claims are addressed after the newly applied 35 U.S.C. 103(a) rejection below.

New Objections/ Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 38 is are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of a specific target, VEGFR1, expression *in vitro*, and for inhibition of VEGFR1 in vivo via injection to the eye with a specific siNA molecule, does not reasonably provide enablement for the treatment of a disease or disorder associated with any target via any means of administration of a pharmaceutical composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The invention of the above claim is drawn to a pharmaceutical composition comprising the double stranded nucleic acid of claim 18 in an acceptable carrier or diluent.

The language "pharmaceutical composition" in claim 38 implies a therapeutic or treatment benefit that is not enabled. The *in vivo* inhibition, treatment, or prevention of target genes described in the specification involves prophetic examples only and have not been reduced to practice. The in vivo example in the specification involves targeting VEGFR1 specifically via injection to the eye and does not enable the scope of the instant claim that is drawn to any target and any means of delivery.

Amendment of the claims to read "A composition comprising the double stranded nucleic acid molecule of claim 18 in a pharmaceutically acceptable carrier or diluent" for example would obviate this rejection.

There is no guidance in the specification as filed that teaches how to target the claimed double stranded nucleic acid molecules to cells or tissues *in vivo*, inhibit the

expression of any target *in vivo*, and further provide treatment for a disease or disorder associated with the target.

The specification does not offer guidance to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the instantly claimed pharmaceutical compositions.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense compounds.

Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies.

The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen et al., who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen et al. concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column)."

As outlined above, it is known that there is a high level of unpredictability in the oligonucleotide art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a therapeutic effect of a double stranded nucleic acid targeted to any target.

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of the double stranded nucleic acid molecule *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of any target gene. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the molecule *in vivo*, delivery of the molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-20, 28, 29, 33, 34, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Bellon et al. (Nucleic Acids Research, 1993, Vol. 21, No. 7, pages 1587-1593), and Hammond et al. (Nature, 2001, Vol. 2, pages 110-119).

The invention of the above claims is drawn to a chemically synthesized double stranded nucleic acid comprising a first and a second strand, wherein the first strand comprises a sense region and the second strand comprise an antisense region, each strand is about 18 to about 27 nucleotides in length, about 18 to about 23 nucleotides of each strand are complementary to each other, and at least 19 nucleotides of the second strand are complementary to a target RNA sequence, and the first strand comprises a terminal cap moiety at the 5' and 3' end and the second strand includes a terminal cap moiety at the 3' end. The invention is further drawn to specific terminal cap moieties, including 4'-thio nucleotides, as well as modifications to the duplex and a pharmaceutical composition comprising the double stranded nucleic acid and a carrier or diluent.

Elbashir et al. teach chemically synthesized 21-nucleotide siRNA duplexes that mediate RNA interference. Elbashir et al. teach a 21-nucleotide siRNA, wherein the first strand is 100% complementary to a target and contains a 2'-deoxythymidine modified overhang (see figure 8, ref). Elbashir et al. teach that multiple 2'-deoxynucleotide substitutions at the 3' end of the duplex are tolerated. The siRNA duplexes taught by Elbashir et al. are assembled from two separate strands, a sense and an antisense

strand. The siRNA duplexes taught by Elbashir et al. comprise one or more ribonucleotides. Elbashir et al. teach 2'-deoxy and 2'-O-methyl modified siRNA duplexes (see page 6881 and figure 4). Elbashir et al. teach duplexes that are 100% modified, which are considered to comprise no ribonucleotides. Elbashir et al. teach successful target inhibition with siRNA duplexes modified at 8 out of 42 nucleotides and teach that complete substitution of the duplex abolishes activity. Furthermore, the instant specification does not define the term "terminal cap". Therefore, the modified terminal nucleotides of the siRNA duplexes of Elbashir et al. meet the instant limitation of including a terminal cap. The reactions taught by Elbashir et al. were carried out in buffers, which are considered pharmaceutically acceptable.

Elbashir et al. does not teach the specific terminal cap moieties recited in instant claim 18.

Bellon et al. teach 4'-thio modified oligonucleotides and teach that such modifications increase resistance to nucleases. Bellon et al. teach that since the majority of antisense molecules are designed to exert their effect upon hybridization to RNA species, the Tm value in conjunction with the high nuclease resistance of 4'-thio modified oligonucleotides suggest that such modifications are a good candidate for providing potential antisense effects.

Hammond et al. teach two methods for silencing specific genes, antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from questionable specificity and incomplete efficacy (see page 110, column 1). Hammond

et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression.

It would be obvious to one of ordinary skill in the art to design a siRNA, as taught by Elbashir et al., wherein both of the strands include 4'-thio terminal cap moieties, as 4'-thio modifications are taught by Bellon et al.

One would have been motivated to design a siRNA of Elbashir et al. specifically including 4'-thio modifications because Bellon et al. teach that 4'-thio modifications increase oligonucleotide resistance to nucleases. Elbashir et al. teach terminal successful terminal modification of siRNA duplexes. Therefore, one would have been motivated to incorporate a specific modification at these terminal locations, such as a 4'-thio modification that was known in the art at the time the invention was made to benefit antisense oligonucleotides by increasing resistance to nucleases.

Hammond et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence specific manner. Hammond et al. teach that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression, thereby offering motivation to utilize dsRNA to inhibit target gene expression rather than a single stranded oligo, as taught by Bellon et al.

This is further evidenced by Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell

type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies and therefore, one would be motivated to incorporate a 4'-thio modification, as taught by Bellon et al., in an attempt to enhance delivery of a siRNA or an antisense oligonucleotide, as each are sequence specific oligonucleotide therapeutics facing the same delivery challenges.

Finally, one would have a reasonable expectation of success given that Elbashir et al. teach successful inhibition of target gene expression via RNAi interference utilizing siRNA duplexes with terminal modifications and Bellon et al. teach that 4'-thio modifications benefit oligonucleotides by increasing resistance to nuclease degradation. One would expect for such modifications to benefit siRNA duplexes because 4'-thio modifications had shown to benefit oligonucleotide therapeutics desiring enhanced delivery.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 18-20 and 28-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al., in view of Bellon et al. and Hammond et al., as explained in the 35 U.S.C. 103(a) rejection above, further in view of Parrish et al.

(Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Schmidt et al. (Nucleic Acids Research, 1996, Vol. 24, No. 4, pages 573-581),

Elbashir et al. does not teach linker molecules or 2'-deoxy-2'-fluoro modifications.

Parrish et al. teach chemically synthesized double stranded siRNA molecules comprising 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand (see figure 5).

Schmidt et al. teach hairpin RNA comprising a sense and antisense region connected via a polynucleotide or non-polynucleotide linker (see Figure 3). Schmidt et al. teach that linkers increase hairpin RNA cleavage efficiencies (see page 575).

It would have been obvious to one of ordinary skill in the art to incorporate polynucleotide or non-nucleotide linkers, as taught by Schmidt et al., and/or 2'-deoxy-2'-fluoro nucleotides, as taught by Parrish et al., into the siRNA molecules taught by Elbashir et al.

One would have been motivated to incorporate the instantly recited modifications into the duplexes taught by Elbashir et al. because Parrish et al. teach the successful application of 2'-deoxy-2'-fluoro modifications in the sense or antisense strand of an siRNA duplex.

Additionally, Schmidt et al. teach hairpin RNA comprising a sense and antisense region connected via a polynucleotide or non-polynucleotide linker (see Figure 3). Schmidt et al. teach that linkers increase hairpin RNA cleavage efficiencies (see page 575). Therefore, one would have been motivated to utilize a hairpin with a linker to increase efficiency of delivery of a dsRNA to a cell.

Finally, one would have a reasonable expectation of success given that both Parrish et al. and Elbashir et al. teach modified siRNA duplexes that achieve inhibition of target gene expression. Therefore, one would expect for the 2'-deoxy-2-fluoro modifications of Parrish et al. to achieve successful inhibition in the duplexes of Elbashir et al. as well. One would reasonably expect for polynucleotide or non-nucleotide linkers as taught by Schmidt et al. to benefit the instant invention since such linkers were known in the art to aid in the production of double stranded RNA molecules.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to 35 U.S.C. 103(a) arguments relevant to the pending claims

Applicant asserts that the examiner suggests that it would have been obvious to try the chemical modifications previously used in connection with ribozyme and antisense art ant that even if this were true, such a position is not the correct standard for judging non-obviousness. Applicant asserts that the subsequent prior art establishes that such suggestions failed in relation to siRNA technology, and this was the status of understanding in the art at the time the invention was made.

Contrary to applicant's assertions, the incorporation of the same chemical modifications for the same reasons into siRNA duplexes that were utilized with ribozyme and antisense therapeutics certainly meets the standard for judging whether the invention is obvious. As explained in the 35 U.S.C. 103(a) rejection above, it was

understood in the art, even after the instant priority date, that dsRNA molecules face the same delivery challenges as other sequence specific inhibitors of target gene expression. Therefore, it would have been obvious to incorporate the same modifications that were known to increase the efficacy of delivery.

Applicant asserts that neither antisense or ribozyme technologies provide any insight or guidance into chemical modification of the siRNAs described by Elbashir et al. and Tuschl et al. On the contrary, the knowledge in the antisense or ribozyme art of the specific modifications that are instantly claimed certainly would motivate one of skill in the art to utilize the same modifications with other molecules that utilize an antisense strand to mediate gene expression to gain the same benefits.

Applicant asserts that siRNAs and ribozymes are not commonly modified. Contrary to applicant's assertions, ribozyme and siRNA modifications are known in the art, as evidenced by the art cited by the examiner above and in the previous office actions. Applicant seems to base this assertion on the teaching of Elbashir et al. that 100% modification of one or both strands abolished activity. Simply because 100% modification abolished activity does not mean that modification of "nucleotides", as instantly claimed, is not a common modification in the art. The instant claims only require that nucleotides are modified.

Additionally, although applicant asserts that the subsequent prior art establishes that such suggestions failed in relation to siRNA technology, this is inconsistent with the teachings relied upon by the examiner. Applicant asserts that the teachings of Elbashir et al. and Tuschl et al. teach away from the invention because 100% modification of one

or both strands abolished activity. On the contrary, the teachings of Elbashir et al. regarding successful inhibition with a siRNA that was modified at 8 out of 42 nucleotides is consistent with the scope of the instant claims. If applicant was claiming 100% modification, than Elbashir et al. would certainly be teaching away from the invention. However, applicant is claiming modification of "nucleotides", which is successfully taught by Elbashir et al.

Applicant asserts that it is impermissible to use hindsight by using the inventors' success as evidence that success would have been expected. It is unclear what is meant by this assertion because the examiner did not rely on teachings by applicant to reach any conclusion. Applicant asserts that it was not known that ribozymes share many of the same chemical modifications as antisense oligonucleotides and siRNA molecules until after the date of the claimed invention. Contrary to this assertion, it was known to utilize the same modifications, as these modifications were taught specifically with regards to siRNA molecules by Elbashir et al. and Parrish et al. before the instant priority date.

With regards to the Declaration under 37 C.F.R. 1.132 filed 3/23/2006, Dr. McSwiggen explains that "there are significant structural differences between antisense oligonucleotides and ribozymes on the one hand and siRNAs on the other". Dr. McSwiggen explains that since siRNAs offer relatively high potency, no stability-inducing modifications would be necessary. To the contrary, the significant structural differences between the molecules are irrelevant to the instant grounds of rejection. The examiner is not relying on any similarity in the structure of the molecules aside from

the fact that each are oligonucleotide therapeutics that act through an antisense strand and face delivery challenges. Although siRNAs may be more potent than antisense oligonucleotides or ribozymes, it is accepted in the art that siRNAs do face the same delivery challenges.

For example, Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies and therefore, one would be motivated to incorporate modifications that were known to benefit previous gene therapy approaches in an attempt to enhance delivery of a siRNA.

Dr. McSwiggen explains that the antisense art and ribozyme art would not supply those skilled in the art with a suggestion or motivation to modify siRNAs in a manner similar to modifications made to antisense oligonucleotides and ribozymes because Elbashir et al. teach a desired protocol in which only the terminal TT was modified. It is noted that the examiner did not rely on antisense or ribozyme art for teaching desired locations of modifications in siRNA duplexes, but rather relied on the art for teaching specific types of modifications that enhance oligonucleotide delivery.

Additionally, Dr. McSwiggen explains that the most relevant art at the time, that is art dealing directly with siRNAs, provided data suggesting that extensive modifications

of siRNAs were undesirable. However, the instant claims are not drawn to "extensive" modification of siRNAs, but are rather drawn to modification of any number of nucleotides. Therefore, arguments drawn to such extensive modification are not considered relevant to the instant claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Amy H. Bowman
Examiner
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PRIMARY EXAMINER